REMARKS

Applicants have the pending claims and provided new claims 37 to 70 to more carefully explain and describe the present invention.

These amendments mirror the original claims and follow the advice of the Examiner regarding new claims 37 and 38. The support is found throughout the specification and original claims. No new matter is added to the application.

ELECTION

The Examiner states that:

"Applicants election of Group I with traverse is acknowledged, as is the elected specie. Applicants have argued that the non-elected claims are part of the same invention as the elected claims. Applicants have stopped short, however, of admitting that claims 17-18 are obvious over claims 1-16, 19-28 or *vice versa*. The absence of such an admission is regarded as a recognition on the part of applicants that Groups I and II are indeed distinct. Applicants have also argued that the fees required of the applicant to file a divisional application would not be in the public interest. However, applicants have not explained how the public would be adversely affected by the filing of a divisional application.

The restriction requirement between Groups I and II is maintained. Claims 17, 18 and 33 are withdrawn from consideration."

Applicants still traverse this restriction and reserve the rights to file divisional and continuation application for rights consistent with the scope of the originally filed specification and claims.

Any amendments made herein are not to be considered a waiver or estoppel for obtain these broader rights in later filed applications.

The amendments are not be construed that Applicants agree with the Examiner's assertions regarding rejections or enablement.

REJECTION CLAIMS 2-16, 24-32 AND 34-36 UNDER 35 U.S.C. 112 (FIRST PARAGRAPH)

"Claims 2-16, 24-32, 34-36 are rejected under 35 U.S.C. 112, first paragraph, as

containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention."

The Examiner states that:

"Applicants have shown that representative examples of the claimed compounds can inhibit caspases *in vitro*. It is stipulated the the following two claims are enabled:

A method of inhibiting a caspase comprising administering a compound according to claim 1 to a human subject in need thereof for a time and under conditions effective to inhibit a caspase.

A method of inhibiting apoptosis comprising administering a compound according to claim 1 to a human subject in need thereof for a time and under conditions effective to inhibit caspase.

However, enablement is lacking for the claimed invention. Applicants are extrapolating from a showing of caspase inhibition *in vitro* to an assertion that all of the following diseases can be successfully treated: arthritis, metastasis, infectious diseases, meningitis, salpingitis, septic shock, respiratory diseases, inflammatory condition, cholangitis, colitis, encephalitis, endocerolitis, hepatitis, pancreatitis, reperfusion injury, ischemic diseases, myocardial infarction, stroke, ischemic kidney disease, immune-based diseases, hypersensitivity, auto-immune diseases, multiple sclerosis, bone diseases, neurodegenerative diseases, Alzheimer's Disease, Amylotrophic Lateral Sclerosis (ALS), Hungtington's disease, Parkinson's disease, meningitis, spinal chord injuries, liver damage, traumatic brain injury, alopecia, AIDS and toxin-induced liver disease.

It is stipulated that some degree of inhibition of caspases will occur *in vivo*. However, enablement is lacking for the claimed invention. As stated in *Ex parte Forman* (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence of absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability of the art, and breadth of the claims.

Consider, for example, the following:

- Frost, Robert A (*American Journal of Physiology. Regulatory, Integrative and Comparative Physiology* 283 (3) R698-709, 2002) investigated the regulation of TNFα and IL-6 by lipopolysaccharide (LPS) in C2C12 myoblasts and mouse

skeletal muscle. Treatment of myocytes with IL-1 or TNF-alpha also increased IL-6 mRNA content, and the increase in IL-6 mRNA due to LPS could not be prevented by pretreatment with antagonists to either IL -1 or TNF. Thus, even if applicants could successfully block all interleukin-1 production using the claimed compounds, interleukin-6 levels could not be controlled, thereby leading to "unpredictable" results on inflammatory response.

- Meyers, K. P. (*Inflammation* 17 (2) 121-34, 1993) discloses that interleukin-1 receptor antagonist was not active as an antiinflammatory agent in the 24-h pleurisy model (carageenan-induced pleurisy).
- Rosenbaum J. T. (*Archives of Ophthalmology* 110 (4) 547-9, 1992) discloses that interleukin-1 receptor antagonist did not produce significant reduction in inflammation subsequent to an active Arthus reaction or subsequent to the intravitreal injection of 125 ng of endotoxin. Rosenbaum suggests that the failure of IL-1RA to be therapeutically effective may be due in part to the presence of other pro-inflammatory cytokines.
- Brennan (*Clinical and Experimental Immunology* 81, 278-85, 1990) discloses that TGF-β was effective to inhibit IL-1β production in LPs-stimulated peripheral blood mononuclear cells, but only if the cells were pretreated with TGF-β. The IL-1β production was not inhibited if the TGF-β was applied after the inducing stimulus. The point here is that if a scientist has evidence that a given agent "X" is effective to inhibit production of IL-1β when used prior to stimulation of cells (which stimulation produces the IL-1 β), attempting to inhibit production of IL-1 β by using agent "X" after stimulation of the cells leads to "unpredictable" results.
- Paris (*Journal of Infectious Diseases* 171, 161-69,1995) discloses that IL-1RA was not effective to treat inflammation caused by gram-negative bacteria.

If it were really true that inhibiting the production of interleukin-1 were effective to treat inflammatory conditions, then the skilled artisan would have expected therapeutic success to follow inevitably from such inhibition, or from inhibiting the activation of the receptor for IL-1. However, this is not what one finds. Accordingly, the skilled artisan would expect that in endeavoring to treat inflammatory disorders using compounds that mitigate the production of or efficacy of IL-1, "unpredictable" results will be obtained. Consider also the following:

- Saez-Torres (*Clinical and Experimental Immunology* 121, 151, 2000 discloses that peptide T inhibits T cell activation and cytokine production, but that it was not effective in vivo to treat EAE (experimental automimmune encephalomyelitis). This supports the assertion that where inflammation and neurodegenerative disorders are concerned, one cannot "predict" therapeutic efficacy on the basis of an *in vitro* assay.

- Hill P. A., (*J Cell. Biochem* 56(1) 118-30, 1994) discloses that a peptide inhibitor of cysteine proteases is not an effective inhibitor of bone resorption. Thus, one cannot predict the propensity of a compound to inhibit bone resorption based on its propensity to inhibit a thiol protease.
- Steinberg (*The Scientist* 16, 22, 2002) discloses that when researchers vaccinated transgenic mice that had developed AD-like pathology, placques "melted away". In addition, favorable results were obtained in cognitive experiments with the mice. However, when attempted in humans, the Alzheimer's disease is concerned, extrapolation from experimental result in animals to humans leads to unpredictable results. Steinberg went much further than applicants have, in that he carried out experiments in animals. If extrapolating from rats to humans leads to unpredictable results, it stands to reason that extrapolating from the test tube to diseased humans will also lead to unpredictable results.
- Kitazawa R (*Journal of Clinical Investigation* 94 (6) 2397-406, 1994) investigated factors affecting osteoclastogenesis. Kitazawa discloses that anti-IL-6 Ab inhibited bone resorption *in vitro* but not *in vivo*. Thus, where bone disease is concerned, the skilled artisan would conclude that in attempting to extrapolate form the petri dish to the human, "unpredictable" results are obtained.
- Read S.J. (*Drugs and Aging* 14 (1) 11-39, 1999) discloses (e.g., abstract) that although many drugs are effective in animal models of cerebral ischemia, these drugs have largely failed to fulfill their promise in clinical trials. Applicants have argued that if a compound can inhibit a caspase in vitro, it will be effective to treat ischemia in a human. However, given that extrapolation from animals to humans leads to unpredictable results, it stands to reason that extrapolating from the test tube to diseased humans will also lead to unpredictable results.

Applicants are also asserting that they can successfully treat any and all "infectious diseases". The nature of such diseases is not specified but would include diseases resulting from a bacterial infection, such as one of the following: Anthrax, Bovine Spongiform, Encephalopathy (BSE), Chicken Pox, Cholera, Conjunctivitis, Creutzfeldt-Jakob Disease, Polio, Nosocomial Infections, Otitis Media, Pelvic Inflammatory disease, Plague, Pneumonia, Dengue Fever, Elephantiasis, Encephalitis, Fifth's Disease, Rabies, Rheumatic Fever, Roseola, Rubella, Sexually Transmitted diseases, Helicobacter Pylori, Smallpox, Strep Throat, septicemia, sickle cell anemia, ulcers, Tetanus, Toxic Shock Syndrome, Lassa Fever, Leprosy, Lyme Disease, Typhoid Fever, Measles, Meningitis, Trachoma, Toxoplasmosis, Tuberculosis, Whooping Cough, and Yellow Fever. In addition to the foregoing, viral infections (e.g., hepatitis, HIV, picornavirus) and fungal infections (e.g. candida albicans) would be included. Diseases resulting from parasitic infections would also be included, such as malaria, trypanosomiasis, schistosomiasis, onchocerciasis, leishmaniasis, amebiasis, ascariasis, babesiosis, balantidiasis, enterobius, fiarisis, blood flukes, giaridasis, hookworm, strongyloidiasis, tapeworm, toxoplasmosis, trichinosis, and trichuriasis.

As it happens, there is "unpredictability" here too. The following references pertain to fungal infections:

- Buchta, V. (*Mycoses* 44 (11-12) 505-12,2001) discloses that a patient died from a fungal infection despite being treated with compounds that exhibit anti-fungal activity *in vitro*.
- Adam (*Medicine* 65, 203, 1986) discloses (page 208, col 2) that *in vitro* susceptibility to antifungal agents did not correlate with therapeutic efficacy of the agents.
- Nagasawa M. (*Journal of Infection* 44 (3) 198-201, 2002) discloses that a patient died from a fungal infection despite being treated with compounds that exhibit anti-fungal activity *in vitro*.
- Manfredi R (*Mycopathologia* 148 (2) 73-8, 1999) discloses that two patients died from a cyrotpococcus infection despite being treated with an agent that exhibited anti-fungal activity *in vitro*.
- Wang M. X. (*Cornea* 19 (4) 558-60, 2000) discloses that a patient was treated with an agent that exhibited anti-fungal activity *in vitro*, but that despite this, his fungal sclerokeratitis progressed to endophthalmitis.
- Bhalodia M V (*Journal of the Association for Academic Minority Physicians* 9 (4) 69-71, 1998) discloses that a compound that exhibited anti-fungal activity *in vitro* was not effective to treat a candida infection in a patient.
- Moore M. L. (*Journal of Perinatology* 21 (6) 399-401, 2001) discloses that a premature infant died from a fungal infection despite being treated with a compound that exhibits anti-fungal activity *in vitro*.
- Berman, Judith (*Nat Rev Genet* 3 (12) 918-30, 2002) discloses that many immunocompromised patients die from *Candida* infections in spite of having received various dosages of compounds which exhibit anti-fungal activity *in vitro*.
- van Duin David (*Antimicrobial Agents and Chemotherapy* 46 (11) 3394-400, 2002) has disclosed an example of a compound which exhibits antifungal activity *in vitro* but not *in vivo*.
- Marr K. A. (*Antimicrobial Agents and Chemotherapy* 45 (1) 52-9, 2001) discloses that a patient developed a fungal infection despite prophylactic treatment with a compound which exhibits antifungal activity *in vitro*.

Thus, even if applicants had demonstrated that the claimed compounds can inhibit growth of fungi *in vitro*, it would still follow therefrom that successful treatment of "infections" in animals could not be predicted. "Infections", of course, would include those caused by bacteria. For example, the following would be encompassed:

Anthrax, cholera, conjunctivitis, nosocomial infections, otitis media, pelvic inflammatory

> disease, plague, pneumonia, dengue fever, elephantiasis, rabies, rheumatic fever, roseola, rubella, syphillis, gonnorhrea, clamydia, helicobacter, pylori, "mucosa-associated lymphoid tissue" resulting from helicobacter pylori, smallpox, strep throat, septicemia, sickle cell anemia, ulcers, tetanus, toxic shock syndrome, lassa fever, leprosy, lyme disease, typhoid fever, measles, meningitis, trachoma, toxoplasmosis, tuberculosis, whooping cough, yellow fever, vancomycin-resistant staphylococcus, diarrhea, brucellosis, diptheria, coccidiodiomycosis, and cold sores.

It is not apparent that any of these diseases can be successfully treated by the claimed compounds. The reality is that attempting to extrapolate from *in vitro* data to a therapy in humans (or other mammals) leads to "unpredictable" results. For example, Otvos "Insect peptides with improved protease-resistance protect mice against bacterial infection" (*Protein Science* 9 (4) 742-9, 2000) discloses one peptide that is active *in vitro* but not *in vivo* (due to the rapid decomposition in mamalian sera). In the field of ulcer treatment, one may look to the following references, which disclose "failure" in the treatment of such, in spite of *in vitro* efficacy in inhibition of *Helicobacter*:

> Phillips, (*Helicobacter* 6, 151, 2001);
> Pilotto (*Digestive and Liver Disease* 32 (8) 667-72, 2000);
> Leung (*Expert Opin Pharmacother* 1 (3) 507-14, 2000).

As for the issue of antibiotic resistance, the following references discuss this:

> Liu (*Advances in Experimental Medicine and Biology* 455, 387 1999)
> Monroe (*Current Opinion in Microbiology* 3(5) 496-501, 2000)

Specifically with regard to endotoxin-associated conditions, consider the following: Corriveau C. C. "Antiendotoxin therapies for septic shock" (*Infectious Agents and Disease*, 2 (1) 44-52, 1993) discloses that there have been numerous attempts over the years to treat human septic shock by inhibiting, neutralizing, or clearing endotoxin, and that the results of those attempts support a conclusion of "unpredictability" in the treatment of the same.

Thus, extrapolation from *in vitro* data to a therapy in humans (or other mammals) leads to "unpredicatable" results.

The pharmaceutical composition claims are rejected because the term "pharmaceutical" implies an assertion of therapeutic efficacy. It is suggested that the existing method claims be cancelled, and that the term "pharmaceutical" be deleted at every occurrence."

Applicants respectfully traverse this rejection. Applicants have cancelled the pending claims 1-36 without prejudice or disclaimer. New claims 37 to 71 are presented for examination. Claims 37 and 38 are the method claims suggested by the Examiner. The remaining claims are

dependent claims with these amendments. Applicants argue that all of the Examiner's concerns have been met and the rejections overcome.

Reconsideration and withdrawal of this rejection is respectfully requested.

REJECTION OF CLAIMS 1-16, 19-35 AND 34-36
UNDER 35 U.S.C. 112 (SECOND PARAGRAPH)

"Claims 1-16, 19-32, 34-36 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention."

The Examiner states that:

– "In the structures of claims 1, 2, 24 a hydrogen atom is missing from each of the amid nitrogens. Hydrogen atoms are also missing from a few of the structures in claim 16."

RESPONSE: Applicants have made these amendments as needed.

– "Claim 2 recites "a pharmaceutical composition for use as a protease inhibitor". However, the intended use is unclear. The term "pharmaceutical" implies an assertion of therapeutic efficacy. This is not enabled, although that is not the point. The point here is that it is unclear how or why one would use a therapeutically effective drug (if one were indeed in possession of such) to inhibit a protease."

RESPONSE: Applicants have made the amendments by presenting method claims.

– "In two of the structures of claim 16 (page 67), an isomer of indole is depicted in which the nitrogen atom bonded to the phenyl ring is in a Schiff Base linkage, and there is an sp^3-hybridized carbon atom within the pyrrole ring. It appears that what is intended instead is an indole structure, as is depicted in the other two structures on page 67."

RESPONSE: Applicants have amended these structures as suggested by the Examiner.

– "Claim 16 is indefinite as to the manner in which, or the extent to which an enzyme would have to resemble a caspase in order for it to qualify as "caspase-like"."

RESPONSE: Applicants have provided amended text in the new claims.

– "In Claim 16, complete structures should be provided. As matters currently stand, applicants are commingling various abbreviations with structures of functional groups."

RESPONSE: Applicants have amended these claims to provide more complete structures as suggested by the Examiner.

– "The method claims are indefinite as to what is meant by an "immune-based disease". In traversing this rejection, applicants are requested to provide two or three examples of diseases which they believe are in no way influenced by, or interface with, the immune system. Such examples will provide the basis for further discussion."

RESPONSE: Applicants have amended the terms to provide the definition requested by the Examiner.

Applicant respectfully traverses these informality rejections.

Applicant has amended the pending claims as suggested by the Examiner. Therefore these rejections have been overcome.

Reconsideration and withdrawal of the rejections are respectfully requested.

SUMMARY

Based on the above amendments and arguments. Applicant asserts these claims are of a form and scope for allowance.

Prompt notification therefore is respectfully requested.

If additional fees are required for the filing of this document, the Commissioner for Patents is hereby authorized to charge or credit overpayment to Deposit Account No. 16-1331.

Respectfully submitted,

Date: June 1, 2004

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